PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 August 2000 (22.08.00)	
International application No. PCT/NL98/00579	**Applicant's or agent's file reference** BO 42135
International filing date (day/month/year) 08 October 1998 (08.10.98)	**Priority date** (day/month/year)
Applicant POELSTRA, Klaas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 May 2000 (04.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/[illegible]

PCT/NL98/00579

[illegible]ATENT COOPERATION TRE[illegible]Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DE BRUIJN, Leendert, C.
Nederlandsch Octrooibureau
Scheveningseweg 82
P.O. Box 29720
NL-2502 LS The Hague
PAYS-BAS

Date of mailing (day/month/year)	
20 April 2001 (20.04.01)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
BO 42135	
International application No.	**International filing date** (day/month/year)
PCT/NL98/00579	08 October 1998 (08.10.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
RIJKSUNUVERSITEIT TE GRONINGEN P.O. Box 72 NL-9700 AB Groningen Netherlands	NL	NL
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
RIJKSUNIVERSITEIT TE GRONINGEN P.O. Box 72 NL-9700 AB Groningen Netherlands	NL	NL
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. Chrem
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003976185

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* BO 42135

Box No. I TITLE OF INVENTION Peptide-based carrier devices for stellate cells and other cell types involved in chronic inflammatory and fibrotic disorders

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Stichting voor de Technische Wetenschappen
P.O. Box 3021
NL-3502 GA UTRECHT
The Netherlands

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: The Netherlands (NL)

State *(that is, country)* of residence: The Netherlands (NL)

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Rijksunuversiteit te Groningen
P.O. Box 72
NL-9700 AB GRONINGEN
The Netherlands

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: The Netherlands (NL)

State *(that is, country)* of residence: The Netherlands (NL)

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DE BRUIJN, Leendert C. et al
Nederlandsch Octrooibureau
Scheveningseweg 82, P.O. Box 29720
NL-2502 LS The Hague
THE NETHERLANDS

Telephone No. 70 3527500

Facsimile No. 70 3527528

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

POELSTRA, Klaas
Kruirad 2
NL-9285 MT BUITENPOST
The Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: The Netherlands (NL)

State *(that is, country)* of residence: The Netherlands (NL)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BELJAARS, Eleonora
Schoolstraat 27 A
NL-9712 JR GRONINGEN
The Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: The Netherlands (NL)

State *(that is, country)* of residence: The Netherlands (NL)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MEIJER, Dirk Klaas Fokke
Parklaan 17
NL-9724 AN GRONINGEN
The Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: The Netherlands (NL)

State *(that is, country)* of residence: The Netherlands (NL)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a C ntracting State of the Harare Protocol and f the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AL** Albania .....
- ☒ **AM** Armenia .....
- ☒ **AT** Austria .....
- ☒ **AU** Australia .....
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina .....
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria .....
- ☒ **BR** Brazil .....
- ☒ **BY** Belarus .....
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China .....
- ☒ **CU** Cuba .....
- ☒ **CZ** Czech Republic .....
- ☒ **DE** Germany .....
- ☒ **DK** Denmark .....
- ☒ **EE** Estonia .....
- ☒ **ES** Spain .....
- ☒ **FI** Finland .....
- ☒ **GB** United Kingdom
- ☒ **GE** Georgia .....
- ☒ **GH** Ghana .....
- ☒ **GM** Gambia
- ☒ **GW** Guinea-Bissau .....
- ☒ **HR** Croatia
- ☒ **HU** Hungary .....
- ☒ **ID** Indonesia
- ☒ **IL** Israel .....
- ☒ **IS** Iceland
- ☒ **JP** Japan .....
- ☒ **KE** Kenya .....
- ☒ **KG** Kyrgyzstan .....
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea .....
- ☒ **KZ** Kazakhstan .....
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho .....
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MD** Republic of Moldova .....
- ☒ **MG** Madagascar .....
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☒ **NO** Norway
- ☒ **NZ** New Zealand .....
- ☒ **PL** Poland .....
- ☒ **PT** Portugal .....
- ☒ **RO** Romania
- ☒ **RU** Russian Federation .....
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia .....
- ☒ **SK** Slovakia .....
- ☒ **SL** Sierra Leone
- ☒ **TJ** Tajikistan .....
- ☒ **TM** Turkmenistan .....
- ☒ **TR** Turkey .....
- ☒ **TT** Trinidad and Tobago .....
- ☒ **UA** Ukraine .....
- ☒ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☒ **UZ** Uzbekistan .....
- ☒ **VN** Viet Nam .....
- ☒ **YU** Yugoslavia .....
- ☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ GD GRENADA .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EPA

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	17
claims	:	8
abstract	:	
drawings	:	6
sequence listing part of description	:	
Total number of sheets	:	35

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract: 35

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

JORRITSMA, R.

8 October 1998

Nederlandsch Octrooibureau, The Hague

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex t the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: BO 42135

Applicant: Stichting voor de Technische Wetenschappen & Rijksuniversiteit Groningen

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 110 [T]
2. SEARCH FEE . . . . . 2510 [S]

International search to be carried out by EPO

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 35 sheets.

first 30 sheets . . . . . 900 [b_1]

5 (remaining sheets) x 21 (additional amount) = 105 [b_2]

Add amounts entered at b_1 and b_2 and enter total at B . . . . 1005 [B]

Designation Fees

The international application contains all designations

_____ (number of designation fees payable *(maximum 11)*) x 208 (amount of designation fee) = _____ [D]

Add amounts entered at B and D and enter total at I . . . . . 1005 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT . . . . . [P]

TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box . . 3625 TOTAL

[X] The designation fees are not paid at this time.

MODE OF PAYMENT

[X] authorization to charge deposit account (see below)	[ ] bank draft	[ ] coupons
[ ] cheque	[ ] cash	[ ] other *(specify)*:
[ ] postal money order	[ ] revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ NL

[X] is hereby authorized to charge the total fees indicated above to my deposit account.

[X] is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

[X] is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

JORRITSMA, Ruurd

15.3.0/0	8 October 1998	
Deposit Account Number	Date *(day month year)*	Signature

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: BO 42135 EE

Applicant: Stichting voor de Technische Wetenschappen et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . [T]

2. SEARCH FEE . . . . . [S]

International search to be carried out by _____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains _____ sheets.

first 30 sheets . . . . . [b1]

_____ (remaining sheets) x _____ (additional amount) = [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . [B]

Designation Fees

The international application contains 5 designations.

5 (number of designation fees payable *(maximum 11)*) x 209 (amount of designation fee) = 1045 [D]

Add amounts entered at B and D and enter total at I . . . . . 1045 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . [P]

5. TOTAL FEES PAYABLE . . . . . 1045 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☒ authorization to charge deposit account (see below)
- ☐ bank draft
- ☐ coupons
- ☐ cheque
- ☐ cash
- ☐ other *(specify)*:
- ☐ postal money order
- ☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ NL

- ☒ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

15.3.0/0	8 October 1999	BOTTEMA, Hans J.
Deposit Account No.	Date *(day/month/year)*	Signature

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

DE BRUIJN, Leendert, C.
Nederlandsch Octrooibureau
Scheveningseweg 82
P.O. Box 29720
NL-2502 LS The Hague
PAYS-BAS

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 28 January 2000 (28.01.00)	
Applicant's or agent's file reference BO 42135	**IMPORTANT NOTIFICATION**
International application No. PCT/NL98/00579	**International filing date** (day/month/year) 08 October 1998 (08.10.98)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SCHUPPAN, Detlef, Bruno, Igor Baumzeil 2 D-91088 Bubenreuth Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
New applicant/inventor for the United States only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 G neva 20, Switz rland**	Authorized officer Athina Nickitas-Etienne
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BO 42135		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL98/00579	08/10/1998	08/10/1998

International Patent Classification (IPC) or national classification and IPC
A61K47/48

Applicant
STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/05/2000	16.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Korsner, S-E T lephone No. +49 89 2399 8554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL98/00579

I. Basis f th r p rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-17	as originally filed				

Claims, No.:

1-26	as received on	18/12/2000	with letter of	18/12/2000	

Drawings, sheets:

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26 (but see V:1)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26 (but see V:2)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26 (see Rule 67.1(iv) PCT for Claims 2-7 and 26)
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
s separate sheet

V. Reasoned statement

Initial remark:
The claimed subject-matter (as amended) relates to two kinds of compounds which are capable of targeting cells involved in sclerotic and/or fibrotic diseases:

A) a receptor (unspecified) binding peptide linked to a carrier, said peptide comprising a cyclic sequence including RGD, KPT, RKKP or SRNLIDC.

B) a mannose-6-phosphate receptor binding compound (unspecified; with a disclaimer) linked to a carrier, characterised by at least 10 molecules/carrier, the compound being in particular mannose-6-phosphate.

The cited prior art is silent about the present concept and the amended set of claims has therefore been accepted under Rule 13 [Unity] in spite of the different types of compounds.

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The following documents will be referred to in this report:

D1 = Hepatology; 1998, page 233A
D2 = Hepatology; 1998, page 313A
D3 = EP - A - 844 252

1. Novelty (Article 33(2) PCT)

I.
Although cited as X-documents, it is presumed by the Examiner that D1-D2 were in fact published on or after the priority/filing date (08.10.98).

The Support Service has not been able to establish the exact date of publication of D1-D2 and this question should be settled at a later stage.

II.
Disregarding D1-D2, the claimed subject-matter is novel over the prior art.

2. Inventive step (Article 33(3) PCT)

It is considered that both A and B fulfill the requirements for an inventive step because it could not have been derived from the cited prior art that these compounds are useful for targeting said cells.

Note that an objection was initially raised against the original drafting of B, "a molecule capable of recognizing and binding mannose-6-receptor" (being undefined and speculative), but the drafting has been modified by the reference to "...at least 10 molecules...".
Whether this amendment is allowable (see VIII:2) and sufficient will be subject to national/regional regulations.

VIII. Certain observations

Claims:

1.
Claims 2-7 and 26 cover methods for treatment, see Rule 67.1(iv) PCT, and are not acceptable under all national/regional regulations (see e.g. Article 52(4) EPC).
In case of a later European phase, the claims could be redrafted with a view to the Guidelines, C-IV, 4.2.

2.
Claims 1-2 and 8-9 refer to "...at least 10 molecules..."; this is derived from Figure 5 and is only valid for mannose-6-phosphate (Claim 9).
The generalisation made in said Claims 1-2 and 8 is not supported by a specific teaching in the Description.

3.
Claims 18-21 should apparently refer to Claims 10-17 (instead of 8-17).

4.
Claim 24 is unclear with regard to the number of carriers because the compound of Claims 8-23 already contains a carrier.

5.
The disclaimer in Claim 25 appears superfluous since the sequence differ from that of the peptide of Claim 11.

Description:

6.
The reason for the disclaimers in Claims 8 and 25 should be explained in the Description.

7.
The claims have been considerably amended during the international phase and the Description should therefore be adapted to the amended set of claims.
Statements such as that on page 4, lines 10-14, should be modified - all those compounds are not inventive (see i.a. D3 which discloses that RGD-containing cyclic peptides bind to receptors; col. 7).
The inventive contribution is that disclosed on page 2, lines 14-15, with an appropriate broadening.

- - -

CLAIMS

1. Method for targeting cells involved in sclerotic and/or fibrotic diseases in a tissue sample of a subject using a carrier molecule, said carrier molecule being linked to at least one further molecule, said further molecule being selected from the group comprising:
- a cyclic peptide comprising the amino acid sequence RGD
- a cyclic peptide comprising the amino acid sequence KPT
- a cyclic peptide comprising the amino acid sequence RKKP
- a cyclic peptide comprising the amino acid sequence SRNLIDC
- a molecule capable of recognising and binding mannose-6-phosphate receptor and at least an amount that is equivalent to at least 10 molecules capable of recognising and capable of binding mannose-6-phosphate receptor linked to HSA are linked to the carrier molecule.

2. Method for targeting cells involved in sclerotic and/or fibrotic diseases in a subject using, in a pharmaceutically acceptable amount and form a carrier molecule, said carrier molecule being linked to at least one further molecule, said further molecule being selected from the group comprising:
- a cyclic peptide comprising the amino acid sequence RGD
- a cyclic peptide comprising the amino acid sequence KPT
- a cyclic peptide comprising the amino acid sequence RKKP
- a cyclic peptide comprising the amino acid sequence SRNLIDC
- a molecule capable of recognising and binding mannose-6-phosphate receptor and at least an amount that is equivalent to at least 10 molecules capable of recognising and capable of binding mannose-6-phosphate receptor linked to HSA are linked to the carrier molecule.

3. Method according to claim 1 or 2 wherein the cells comprise at least one target receptor specific for Hepatic Stellate Cells (HSC) or a receptor that is upregulated on HSC during disease.

4. Method according to any of claims 1-3 wherein the cells comprise at least one target receptor selected from the group of PDGF receptor, collagen type VI receptor, cytokine receptor(s) such as TGFß, TNFα and interleukin 1ß.

5. Method according to any of the claims, wherein the carrier molecule comprises additional drugs or chemicals linked thereto.

6. Method according to any of the preceeding claims, wherein the carrier molecule comprises a diagnostic marker attached thereto.

7. Method according to any of the preceeding claims wherein the cells involved in a sclerotic and/or a fibrotic disease are cells involved in a disease selected from the group consisting of liver fibrosis, in particular cirrhosis, kidney fibrosis, in particular glomerulosclerosis and interstitial fibrosis, lung fibrosis, atherosclerosis and chronic or acute inflammatory processes such as rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis, sepsis and tumor-cell proliferation associated pathology, fibroblast proliferation associated pathology, endothelial cell proliferation associated pathology and osteoblast proliferation associated pathology.

8. Compound for use in a method according to claim 1 or 2 said compound being a carrier molecule linked to at least 10 molecules capable of recognising and capable of binding mannose-6-phosphate receptor are linked to the carrier molecule, with the provisio the compound is not a naturally occuring peptide with terminal mannose-6-phosphate residues, latent tumor growth factor beta, thyroglobulin or a lysosomal protein.

9. Compound according to claim 8 wherein the molecule capable of recognising and capable of binding mannose-6-phosphate receptor is mannose-6-phosphate.

10. Compound for use in a method according to any of the claims 1-7 said compound being a carrier molecule linked to at least one further molecule said further molecule being X*YRGDYX*, wherein X* represents the location of cyclisation and Y represents at least one amino acid or a sequence of amino acids up to a length such that the target receptor binding capacity of the further molecule is retained.

11. Compound according to claim 10 wherein said further molecule is X*GRGDSPX*, wherein X* represents the location of cyclisation.

12. Compound for use in a method according to any of claims 1-7 said compound being a carrier molecule linked to at least one further molecule said further molecule being X*YKPTYX*, wherein X* represents the location of cyclisation and Y represents at least one amino acid or a sequence of amino acids up to a length such that the target receptor binding capacity of the further molecule is retained.

13. Compound according to claim 12 wherein said further molecule is X*DKPTLX*, wherein X* represents the location of cyclisation.

14. Compound for use in a method according to any of claims 1-7 said compound being a carrier molecule linked to at least one further molecule said further molecule being X*SRNLIDCX*, wherein X* represents the location of cyclisation.

15. Compound for use in a method according to any of claims 1-7 said compound being a carrier molecule linked to at least one further molecule said further molecule being X*RKKPX*, wherein X* represents the location of cyclisation.

16. Compound according to any of claims 10-15 wherein X* is a cystein residue.

17. Compound according to any of claims 10-16 wherein X* represents the location of cyclisation and attachment to the carrier molecule.

18. Compound according to any of the claims 8-17 wherein of the further molecule the cyclic portion of the cyclic peptide comprises multiple receptor binding sequences.

19. Compound according to any of the claims 8-18 wherein of the further molecule the cyclic portion of the cyclic peptide comprises multiple receptor binding sequences directed at at least two different types of receptors.

20. Compound according to any of the claims 8-19, wherein the further molecule comprises multiple cyclic peptides directed at the same or different types of receptors.

21. Compound according to any of the claims 8-20, wherein the carrier molecule is selected from the group of carrier molecules consisting of proteins, oligo or polypeptides, immunoglobulins or parts thereof, oligonucleotides, disaccharides, polysaccharides, biodegradable synthetic polymers, liposomes, lipid particles, biocompatible polymers in the form of microspheres or nanoparticles, endogenous plasma proteins e.g. albumin, lactoferrin, alkaline phosphatase, superoxide dismutase, alpha2 macroglobulin and fibronectin.

22. Compound according to any of the claims 8-21, wherein the carrier molecule comprises additional drugs or chemicals linked thereto.

23. Compound according to any of the claims 8-23 wherein the carrier molecule comprises a diagnostic marker attached thereto.

24. Pharmaceutical composition comprising a compound according to any of claims 8-23 as targeting ingredient and one or more pharmaceutically acceptable carriers.

25. Use of a compound according to claim 8-23 for in vitro diagnosis of a sclerotic and/or fibrotic disease in particular for in vitro diagnosis of a disease selected from the group consisting of liver fibrosis, in particular cirrhosis, kidney fibrosis, in particular glomerulosclerosis and interstitial fibrosis, lung fibrosis, atherosclerosis and chronic or acute inflammatory processes such as rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis, sepsis and tumor-cell proliferation associated pathology, fibroblast proliferation associated pathology, endothelial cell proliferation associated pathology and osteoblast proliferation associated pathology with the provisio the compound *cyclo*[-D-Val-Arg-Gly-Asp-Glu(-εAhx-Tyr-Cys-NH)-] linked to BSA is not used in a cell adhesion assay for endothelial cells.

26. Use of a compound according to claim 8-23 or a pharmaceutical composition according to claim 24 for in vivo diagnosis, prophylaxis and/or therapy of a sclerotic

and/or fibrotic disease in particular for in vitro diagnosis of a disease selected from the group consisting of liver fibrosis, in particular cirrhosis, kidney fibrosis, in particular glomerulosclerosis and interstitial fibrosis, lung fibrosis, atherosclerosis and chronic or acute inflammatory processes such as rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis, sepsis and tumor-cell proliferation associated pathology, fibroblast proliferation associated pathology, endothelial cell proliferation associated pathology and osteoblast proliferation associated pathology.

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(54) Title: PEPTIDE–BASED CARRIER DEVICES FOR STELLATE CELLS

(57) Abstract

The present invention relates to a compound comprising a carrier molecule, said carrier molecule being linked to a further molecule, said further molecule being at least one cyclic peptide, said cyclic peptide comprising in the cyclic peptide portion thereof at least one sequence encoding a cell receptor recognising peptide (RRP) and with the proviso that the compound is not a naturally occuring receptor agonist or antagonist. Preferably, the RRP is of a receptor specific for Hepatic Stellate Cells (HSC) or a receptor that is upregulated on HSC during disease. In particular, the RRP may be of a receptor selected from the group of PDGF receptor, collagen type VI receptor, cytokine receptor(s) such as TGFβ, IFNα and interleukin 1β. Preferably, the cyclic portion of the cyclic peptide comprises at least the amino acid sequence RGD or KPT. The compounds can be used as an active targeting ingredient for manufacturing a pharmaceutical composition for therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis and sepsis, in particular for targeting HSC. The invention also relates to pharmaceutial compositions comprising the above compound(s).

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PEPTIDE-BASED CARRIER DEVICES FOR STELLATE CELLS

Background of the invention

The hallmark of fibrosis is the excessive deposit of extracellular matrix components caused by an increased synthesis and decreased degradation of matrix proteins, predominantly collagen type I and III. This process of fibrosis can occur in all kinds of organs such as the kidney (glomerulosclerosis or interstitial fibrosis), the skin (scar formation), the lung and also in the liver, where the end-stage of liver fibrosis is referred to as cirrhosis. The process also shares many characteristics with the formation of atherosclerotic plaques in arteries. Liver fibrosis leads to a deterioration of liver function, and eventually in complete liver failure, which is lethal if untreated. The process can be elicited by viruses (Hepatitis A, B and C), alcohol consumption, genetic disorders, or by chronic exposure to hepatotoxic agents. The incidence of this disease is very variable depending on the country. In the period 1985-1989, the incidence of liver cirrhosis in The Netherlands was 3.90 per 100,000 habitants per year, whereas this incidence in, for instance, France and Germany was 11.9 respectively 12.4. To date, no effective pharmacotherapeutic intervention is available for this disease. In the past decades liver transplantation has become a serious option for many patients but the costs, the availability of donor livers and the traumatic event of the transplantation itself hamper the application of such an operation in general practice. Pharmacological intervention would be a better option.

Hepatic stellate cells (HSC), also called Ito cells or fat storing cells strongly proliferate during the progression of the disease and they subsequently transform into myofibroblasts (MF). These cells are the major producers of collagens, glycoproteins, and proteoglycans in a diseased liver. Moreover, HSC and MF produce an array of mediators which activate other hepatic and inflammatory cells thus enhancing the fibrotic process. Therefore, HSC are an important target for anti-fibrotic therapy. However, in vivo studies indicate that anti-fibrotic drugs are not efficiently taken up by HSC and as a consequence, most drugs which showed potent anti-fibrotic activity in vitro, failed to exert any effect in vivo. At high doses such drugs often induce many side effects caused by extrahepatic distribution of the drug. Cell specific delivery is an option to solve these

problems. This can be accomplished by coupling drugs to carrier molecules, which are selectively taken up by the target cells. Liposomes are well known drug carriers but modified proteins can also be applied. Cell specific delivery of therapeutic and diagnostic agents to hepatocytes, endothelial and Kupffer cells has already been achieved by modification of the sugar moieties of proteins or polymers. Coupling of galactose to, for instance, human serum albumin (HSA) leads to a specific accumulation of this neoglycoprotein in hepatocytes whereas addition of mannose to albumin causes uptake into Kupffer or endothelial cells. Increasing the net negative charge (for instance by succinylation of amine groups) results in uptake of the protein into endothelial cells via scavenger receptors. For a comprehensive review on carrier devices for cell specific delivery of drugs see D.K.F. Meijer and G. Molema, Sem. in Liver Dis. 15: 202-256, 1995. The benefits of such carrier devices for the development of novel pharmacotherapeutic interventions for various diseases has been well recognized. However, a specific carrier for drugs to HSC, the most important cell in the pathogenesis of liver fibrosis, has not been found yet.

Summary of the invention

The invention describes novel drug carriers which specifically accumulate in hepatic stellate cells (HSC). These carriers can be used for the targeting of all kinds of therapeutic agents, preferably anti-fibrotic drugs to HSC. The carriers may also be applied for the visualization of HSC for diagnostic purposes. The basis of the invention lies in the coupling of small cyclic proteins (oligopeptides), that contain specific receptor recognising peptides (RRPs) to soluble or particle type carriers (core carriers). The use of such a conjugate as a tool for targeting purposes has not been described. The target-receptors for these neo proteins, neo oligopeptides or oligopeptide carrier constructs are specific for HSC or are upregulated upon this cell type during the course of the disease. In the present study human serum albumin (HSA) is applied as the core-carrier, but the invention is not restricted to a specific protein or polymer. Each molecule with attachment sites for peptides is applicable as a carrier to HSC. The invention describes conjugates which bind to the platelet derived growth factor (PDGF)-receptor and conjugates which attach to the collagen type VI receptor. Both types of receptors are present in relatively high amounts upon HSC and are well characterized. The respective receptor-binding ligands are known.

Since these receptors are also upregulated in renal mesangial cells as well as fibroblasts in various organs during glomerulosclerosis, interstitial fibrosis, lung fibrosis or atherosclerosis, and since these pathological processes are accessible for macromolecules it is assumed that these carriers will also show a relative accumulation in these cell types during the course of these diseases. The conjugates described here may therefore also be applied as drug-carriers or carriers for diagnostic markers and/or for treatment of the above mentioned diseases.

The proliferation of HSC during the process of fibrosis is an important pathogenic factor. Cell-matrix interactions and the production of growth factors such as PDGF play a pivotal role in this proliferative response of HSC. Peptides which bind to the PDGF receptors or collagen type VI receptors will block the binding of endogenous PDGF or will interfere with cell-matrix interactions and therefore the oligopeptides described here may also exert an antiproliferative activity and consequently these oligopeptides may serve as anti-fibrotic or anti-sclerotic agents themselves.

Also other receptors may be targeted using this new approach. Transforming Growth Factor ß (TGFß), interleukin 1ß (Il 1ß), and Tumor Necrosis Factor α (TNFα) are other important mediators during chronic inflammatory processes and the receptors for these cytokines are upregulated upon HSC as well as upon endothelial cells and Kupffer cells in the liver. The ligands for these receptors are well characterized and similar to the PDGF-receptor or collagen VI-receptor recognizing proteins, cyclic peptides recognizing the binding site for these receptors can be prepared and coupled to a core-protein such as albumin. A relative accumulation of these conjugates can be expected into the target cell expressing the particular receptors. Most of the cytokines contain a RGD sequence (arg-gly-asp). This is the (putative) cell attachment site and in combination with additional amino acids it will determine the specificity for the individual cytokines and growth hormone receptors. Coupling this RGD sequence and accompanying amino acids to a carriermolecule using the approach described here is feasible. The invention also includes the preparation of oligopeptides in which more than one receptor recognizing domain for the same receptor are combined and peptide constructs in which different receptor recognizing domains for different types of receptors are combined. The particular oligopeptide constructs containing a single or more than one receptor recognizing domain can be used as such, as intrinsic active substances but also for the preparation of drug conjugates (pro-drugs) and be employed

to prepare larger drug carriers by coupling of the oligopeptides to either proteins, soluble and particulate polymeric carriers and lipoid carriers (liposomes, neolipoproteins, micelles) that subsequently can be used for covalent binding and/or inclusion or association of therapeutic agents for the purpose of cell-specific drug targetting.

The application of such carriers is not limited to the treatment or diagnosis of fibrotic processes but also to other chronic and acute inflammatory processes such as, for instance, rheumatoid arthritis, Crohn's disease, colitis ulcerosa, glomerulonephritis and sepsis.

Detailed description of the invention

A compound according to the invention comprises a carrier molecule, said carrier molecule being linked to a further molecule, said further molecule being at least one cyclic peptide, said cyclic peptide comprising in the cyclic peptide portion thereof at least one sequence containing at least one specific receptor recognising peptide (RRP) and with the proviso the compound is not a naturally occurring receptor agonist or antagonist. Suitably in such a compound according to the invention the RRP is of a receptor specific for Hepatic Stellate Cells (HSC) or a receptor that is upregulated on HSC during disease.

The RRP can by way of example be the agonist or antagonist of a receptor selected from the group of receptors consisting of PDGF receptor, collagen type VI receptor, cytokine receptor such as TGFß, TNFα and interleukin 1ß.

Suitably when the RRP is of a collagen type VI receptor, cytokine receptor such as TGFß, TNFα and interleukin 1ß the cyclic portion of the cyclic peptide comprises at least the amino acid sequence RGD or KPT (lys-pro-thr) in the cyclic portion thereof. By way of example the cyclic portion of the cyclic peptide comprises at least an amino acid sequence selected from X*YRGDYX* (Xaa-$(Xaa)_n$-arg-gly-asp-$(Xaa)_n$ -Xaa) and X*YKPTYX* (Xaa-$(Xaa)_n$-lys-pro-thr-$(Xaa)_n$-Xaa) wherein X* represents the location of cyclisation and Y represents at least one amino acid or a sequence of amino acids up to a length such that the receptor binding capacity of the cyclic peptide is retained. In a preferred embodiment X* represents the location of attachment to the carrier molecule. An embodiment illustrating the above when the receptor agonist is of a collagen type VI receptor has a cyclic portion of the cyclic peptide comprising the amino acid sequence X*GRGDSPX* (Xaa-gly-arg-gly-asp-ser-

pro-Xaa). Suitably it will comprise the sequence -cysteine-glycine-arginine-glycine-aspartic acid-serine-proline-cysteine.

Suitably when the receptor agonist is of a interleukin 1 beta receptor the cyclic portion of the cyclic peptide can comprise the amino acid sequence X*DKPTLX* (Xaa-asp-lys-pro-thr-lys-Xaa).

Alternatively when the receptor agonist is of a PDGF receptor the cyclic portion of the cyclic peptide can comprise the amino acid sequence X*SRNLIDCX* (Xaa-ser-arg-asn-leu-ile-asp-cys-Xaa), wherein X* represents the location of cyclisation.In a preferred embodiment X* represents the location of attachment to the carrier molecule. Such a compound will bind to the PDGF receptor alpha and bèta subtypes. Suitably it will comprise the sequence -cysteine-serine-arginine-asparagine-leucine-isoleucine-aspartic acid-cysteine.

In any of the embodiments according to the invention that are described X* can be a cysteine residue.

Only some crucial amino acids for the cyclic peptides are provided here. The oligopeptide may be elongated without causing a change in the cellular distribution pattern in vivo. Cyclisation of these peptides can be achieved for example by a disulfide bond between both cysteine groups. The free amine (α-amine) in one cysteine residue can be used to couple the oligopeptide to the carrier molecule. For example to the amine groups in a core-molecule like albumin, using succinimide-acetyl thioacetate (SATA). Coupling of more than one oligopeptide to albumin can be readily done. Attachment of the cyclic peptides to a carrier molecule via a biodegradable spacer, causing local release of the cyclic peptides, is also feasible. The examples provided here describe conjugates with multiple oligopeptides per HSA molecule, leaving enough free reactive groups within the core-protein (hydroxyl, amine or sulphate groups) to attach additional drugs or other chemicals. These conjugates selectively accumulate in HSC of normal and diseased livers.

The cyclic portion of the cyclic peptide can suitably comprise multiple RRP sequences. The cyclic portion of the cyclic peptide can comprise multiple RRP sequences directed at at least two different types of receptors. Obviously they can also be directed at the same type of receptor. Combinations of various receptor agonist sequences are naturally also possible. Thus a compound according to the invention in any of the embodiments defined may comprise multiple cyclic peptides directed at the same or

different subtypes of receptors or may comprise multiple but similar oligopeptides that contain more than one identical or different RRP sequence directed at the same receptor or different receptors on the particular cell type respectively. By way of example a compound according to the invention, wherein the carrier molecule is linked to more than one cyclic peptide can suitably comprise 5-15 cyclic peptides as defined in any of the embodiments above.

A person skilled in the art will realise numerous types of carrier molecules can be applied. The carrier molecule can suitably be selected from endogenous plasma proteins e.g. albumin, lactoferrin, alkaline phosphatase, superoxide dismutase, alpha2 macroglobulin and fibronectin. They are to be pharmaceutically acceptable and of a size such that they preferably are not lost due to the renal excretion thereof. Such compounds are suitably larger than 5000 Daltons. Suitable examples of the carrier molecule can be selected from the group of carrier molecules consisting of proteins, oligo or polypeptides, immunoglobulins or parts thereof, oligonucleotides, disaccharides, polysaccharides, biodegradable synthetic polymers, liposomes, lipid particles, biocompatible polymers in the form of microspheres or nanoparticles. Quite suitably in a compound according to this aspect of the invention the carrier molecule is the endogenous plasma protein albumin. The immunoglobulins can be mono or polyclonal. Parts of immunoglobulins can comprise Fab' fragments or single chain Ig. Humanised antibodies and bispecific antibodies are envisaged.In the case of human administration carriers that occur naturally in humans are preferred. For the sake of easy linkage of the carrier molecule to the cyclic peptide the carrier molecule preferably comprises free reactive groups such as hydroxyl, amine or sulphate. The carrier molecule can suitably be linked to the cyclic peptide via a biodegradable spacer. The carrier molecule can itself be a drug, the activity of which is not impaired by linking the cyclic peptide to it.

In an alternative embodiment of the invention the carrier molecule in the compound can comprise additional drugs or chemicals linked thereto.

The invention also covers a pharmaceutical composition comprising a compound according to any of the aforementioned embodiments as targeting ingredient and any pharmaceutically acceptable carrier. A pharmaceutical composition according to the invention comprises a compound in any of the embodiments mentioned above as pharmaceutically active ingredient in combination with any pharmaceutically acceptable additional carrier. In an alternative embodiment the pharmaceutical composition can

further comprise a drug biodegradably attached to the compound. It is also possible for the compound to further comprise a diagnostic marker attached thereto. A pharmaceutical composition according the invention will be in a pharmaceutical dosage form. Such a dosage form can comprise sprayable, injectable or infusable solutions or solids or dosage forms for pulmonary or other administration routes. Also a pharmaceutical composition according to the invention can be in a topical form. In the case of parenteral administration a systemically acceptable form should be composed. This means it can enter the bloodstream without causing clotting or inadmissibly toxic reactions.

The invention is also directed at application of a compound according to the invention in any of the abovementioned embodiments as active targeting ingredient for manufacturing a pharmaceutical composition according to the invention for therapy, prophylaxis or diagnosis of chronic diseases. Examples from this group consist of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis, lung fibrosis and sepsis. Suitably use of a compound according to the invention as active targeting ingredient for manufacturing a pharmaceutical composition according to the invention for therapy, prophylaxis or diagnosis of a disease related to proliferation of HSC is also envisaged as forming a particularly useful application to be covered by the invention. A method of targeting HSC, said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition according to the invention to a subject or a tissue sample of a subject is covered by the invention. The person skilled in the art will adjust the dosage to be applied to the manner of application, size, weight, state of health etc of the subject to which administration is to occur. Administration can ocur in any manner known per se for administration of medicament.

The invention also covers a method of therapy, diagnosis or prophylaxis of a disease related to HSC, said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition according to the invention to a subject or a tissue sample of a subject. Particularly such disease can be one selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa,

glomerulonephritis and sepsis. The method comprises administration in a pharmaceutically acceptable amount and form of the compound or pharmaceutical composition according to the invention to a subject or a tissue sample of a subject. The person skilled in the art will adjust the dosage to be applied to the manner of application, size, weight, state of health etc of the subject to which administration is to occur. Administration can occur in any manner known per se for administration of therapeutic agents.

This further aspect of the invention will be illustrated but not limited in the following examples.

EXAMPLE 1

Normal rats and rats with liver fibrosis (3 weeks after bile duct ligation) received an intravenous injection of 10 mg/kg b.w. PDGF receptor-binding peptides conjugated with HSA. Based upon the results of the organ distribution studies with radiolabeled conjugates (figure 1), rats were sacrificed after ten minutes and samples of the liver and bone (from ribs, front paw, rear paw and the back) were removed for histochemical examination. No accumulation of this HSA-peptide conjugate was detectable in bone samples, whereas abundant staining was found in tissue samples. Upon cryostat sections of these livers double stainings were performed with anti-HSA antibodies and antibodies against Kupffer cells (ED1), endothelial cells (RECA-1), myofibroblasts (anti-actin antibodies) or hepatic stellate cells (desmin and GFAP antibodies). Subsequently, the number of double positive cells (HSA+ and cell marker+) were counted and related to the total number of HSA positive cells in the same area. Results of the quantitative evaluation of the carrier uptake in the liver are summarized in table 1.

Table 1: Relative accumulation of HSA modified with collagen VI-receptor recognising peptides (pCVI-HSA) or PDGF receptor-recognising peptides (pPB-HSA) in non-parenchymal cells of the liver. The number of HSA-positive cells was related to the number of cells double-positive for HSA and a HSC marker (desmine), or a EC marker (HIS 52), or a KC marker (ED2) or a PC marker (glycogen).

	% HSC	% EC	% KC	PC
pCVI-HSA	73 ± 14	30 ± 10	16 ± 11	-
pPB-HSA	72 ± 18	16 ± 6	11 ± 6	+

HSC = hepatic stellate cells, EC = endothelial cells, KC = Kupffer cells, PC = parenchymal cells

EXAMPLE 2

Normal rats and rats with liver fibrosis (3 weeks after bile duct ligation) received an intravenous injection of 10 mg/kg b.w. collagen VI receptor-binding peptides conjugated with HSA. Based upon the results of the organ distribution studies with radiolabeled conjugates (figure 2), rats were sacrificed after ten minutes and samples of the liver and bone (from ribs, front paw, rear paw and the back) were removed for histochemical examination. No accumulation of this HSA-peptide conjugate was detectable in bone samples, whereas abundant staining was found in tissue samples. Upon cryostat sections of these livers double stainings were performed with anti-HSA antibodies and antibodies against Kupffer cells (ED1), endothelial cells (RECA-1), myofibroblasts (anti-actin antibodies) or hepatic stellate cells (desmin and GFAP antibodies). Subsequently, the number of double positive cells (HSA+ and cell marker+) were counted and related to the total number of HSA positive cells in the same area. Results of the quantitative evaluation of the carrier uptake in the liver are summarized in table 1.

EXAMPLE 3

Another cyclic oligopeptide recognizing the PDGF-receptor can be described as follows:

-cysteine-arginine-lysine-lysine-proline-cysteine- (C*RKKPC*),

where the cysteines (C*) represent the cyclisizing residues.

Only some crucial amino acids for the PDGF-binding peptide are provided here. The oligopeptide may be elongated without causing a change in the cellular distribution pattern in vivo. Cyclisation of this peptide can be achieved by a disulfide bond between both cysteine groups, whereas the free amine in one cysteine residue can be used to couple the oligopeptide to a core-molecule like albumin. Coupling of more than one oligopeptide to albumin can be readily done.

EXAMPLE 4

A cyclic peptide which binds to the interleukin 1ß-receptor can be described as follows:

-cysteine-aspartic acid-lysine-proline-threonine-leucine-cysteine- (C*DKPTLC*)

where the cysteines (C*) represent the cyclisizing residues.

The receptor binding properties of the tripeptide lysine-proline-threonine (KPT) has been reported (Ferreira et al., Nature 334: 698, 1988). Two or more additional amino acids, preferably the two adjacent amino acids in the native interleukin 1ß molecule on both sites of this tripeptide, are in this example attached to this tripeptide. Subsequently, the terminal cysteine residues allow for cyclysation of this oligopeptide and coupling of this peptide to a macromolecule. In this way, the interleukin 1ß binding site is exposed to its receptor similar to the PGDF- and collagen VI receptor binding peptides. This conjugate may also serve as a carrier for therapeutic or diagnostic agents for the treatment of inflammatory processes.

DESCRIPTION OF THE DRAWINGS

Fig. 1: Organ distribution of human serum albumin (HSA) conjugated with 10 to 12 cyclic oligopeptides recognizing the PDGF-receptor in normal rats [figure A] and in rats with liver fibrosis induced by bile duct ligation (3 weeks after the operation) [fig.B]. Figure C represents the organ distribution of unmodified HSA. Organs were removed 10 minutes after intravenous administration of radiolabeled (^{125}I) protein and analyzed using a gamma-counter. The results are expressed as the mean ± SD (n=3 per group). Note the accumulation of modified HSA in livers of normal and diseased rats,

whereas native HSA remains in the blood.

Fig. 2: Organ distribution of human serum albumin (HSA) conjugated with 10 to 12 cyclic oligopeptides recognizing the collagen type VI-receptor in normal rats [figure A] and in rats with liver fibrosis induced by bile duct ligation (3 weeks after the operation) [fig. B]. Organs were removed 10 minutes after intravenous administration of radiolabeled (^{125}I) protein and analyzed using a gamma-counter. The results are expressed as the mean ± SD (n=3 per group). Note the accumulation of modified HSA in livers of normal and diseased rats.

Fig. 3: Intrahepatic distribution of HSA modified with 10-12 collagen type VI-receptor binding peptides in fibrotic rats (3 weeks after bile duct ligation). 10 minutes after intravenous administration of modified protein, the albumin derivatives can be imuunhistochemically detected in a non-parenchymal cell type of the liver using a polyclonal antibody against albumin [fig. A]. The modified albumin co-localizes with the marker for HSC (desmin) [see arrowheads, fig. B].

Fig. 4: In vitro displacement of radiolabeled PDGF-BB from its receptor upon 3T3-fibroblasts by HSA-PDGF receptor-binding peptide conjugates (pPB-HSA, closed blocks), HSA (open blocks) or uncoupled PDGF-receptor binding peptides (pPB, open circles). Note the strong inhibition of binding of native PDGF to fibroblasts induced by the modified HSA, but not by native HSA or the oligopeptides alone.

Background information to a further aspect of the invention

An increased expression of the Insulin Growth Factor II/mannose-6-phosphate (IGFII/M6P) receptor has been reported upon hepatic stellate cells in particular after activation of this cell type. This led to the idea of coupling mannose-6-phosphate (M6P) to a core-protein and the use of such a neo-glycoprotein as a drug carrier to HSC. The degree of substitution of M6P to HSA necessary for this purpose could not be deduced from the present state of the art. We have found that a quite high degree of substitution is required for efficient targeting. Introduction of only a few groups was not particularly successful. The invention thus provides a novel type of drug carrier to the hepatic stellate cells (HSC). The carrier can be used for the targeting of all kinds of therapeutic agents, preferably anti-fibrotic agents to HSC, or may be applied for the visualization of HSC for diagnostic purposes.

As it was also reported that this receptor played a role in the activation of latent TGF-beta and TGF-beta is known to be a pro-fibrogenic growth factor which is a very important mediator during fibrosis the compound acording to this further aspect of the invention should also be useful for diagnosis, prophylaxis and therapy of fibrotic diseases. Mannose-6-phosphate substituted proteins may also interfere with the activation of latent TGF-beta and this carrier may therefore have an antifibrotic action of its own.

Detailed description of the further aspect of the invention

The invention in a further aspect is directed at a compound capable of recognising and binding a mannose 6 phosphate receptor said compound comprising a carrier molecule linked to a molecule capable of recognising and capable of binding mannose-6-phosphate receptor, said molecules recognising and capable of binding mannose-6-phosphate receptor being present on the carrier molecule in at least an amount sufficient to occupy at least 20% of the carrier molecule linking sites for said molecules recognising and capable of binding mannose-6-phosphate receptor, with the proviso the compound is not latent tumor growth factor beta, thyroglobulin or a lysosomal protein. The latter are known proteins that are also known to comprise terminal mannose 6 phosphate groups and as such will bind to the mannose 6 phosphate receptor. They are excluded as compounds according to the invention. The substitution degree can be higher than 30% even as high as 40 or 50%. A suitable example of the molecule capable of recognising and capable of binding mannose-6-phosphate receptor is

mannose 6 phosphate.

In a compound according to this aspect of the invention the carrier molecule can be selected from the group consisting of proteins, oligo or polypeptides, immunoglobulins or parts thereof, oligonucleotides, disaccharides, polysaccharides, biodegradable synthetic polymers, liposomes, lipid particles, biocompatible polymers in the form of microspheres or nanoparticles. The carrier molecule can suitably be selected from endogenous plasma proteins e.g. albumin, lactoferrin, alkaline phosphatase, superoxide dismutase, alpha2 macroglobulin and fibronectin. The immunoglobulins can be mono or polyclonal. Parts of immunoglobulins can comprise Fab' fragments or single chain Ig. Humanised antibodies and bispecific antibodies are envisaged. Quite suitably in a compound according to this aspect of the invention the carrier molecule is the endogenous plasma protein albumin. A person skilled in the art will realise numerous types of carrier molecules can be applied. They are to be pharmaceutically acceptable and of a size such that they preferably are not lost due to the renal excretion thereof. Such compounds are suitably larger than 50000 Daltons.

Quite specifically in a preferred embodiment of a compound according to this aspect of the invention at least 10 molecules capable of recognising and capable of binding mannose-6-phosphate receptor are linked to the carrier molecule. The carrier based upon macromolecules substituted with mannose-6-phosphate residues with substitution of more than 10 mannose-6-phosphate residues per macromolecule has been found exceptionally appropriate for proper targeting. The carrier molecule was human serum albumin.

The invention also covers a pharmaceutical composition comprising a compound according to any of the aforementioned embodiments of the further aspect of the invention disclosed as targeting ingredient and any pharmaceutically acceptable carrier. A pharmaceutical composition according to the invention comprises a compound in any of the embodiments mentioned above as pharmaceutically active ingredient in combination with any pharmaceutically acceptable additional carrier. In an alternative embodiment the pharmaceutical composition can further comprise a drug biodegradably attached to the compound. It is also possible for the compound to further comprise a diagnostic marker attached thereto. A pharmaceutical composition according the invention will be in a medicinal dosage form. Such a dosage form can comprise sprayable, injectable or infusable solutions or solids or dosage forms for pulmonary or

other administration routes. Also a pharmaceutical composition according to the invention can be in a topical form but will preferably be in a systemically acceptable form. This means it can enter the bloodstream without causing clotting or inadmissibly toxic reaction.

The invention is also directed at application of a compound according to the invention in any of the abovementioned embodiments as active targeting ingredient for manufacturing a pharmaceutical composition according to the further aspect of the invention just mentioned for therapy, prophylaxis or diagnosis of a disease selected from the group of chronic diseases, for example fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis and sepsis.

The invention is also directed at application of a compound according to the invention in any of the abovementioned embodiments as active targeting ingredient for manufacturing a pharmaceutical composition according to the further aspect of the invention just mentioned for therapy, prophylaxis or diagnosis of any of the following pathological conditions; cell proliferation associated pathology e.g. tumors, a disease related to proliferation of HSC, fibroblast proliferation associated pathology, endothelial cell proliferation associated pathology and osteoblast proliferation associated pathology. The invention also covers a method of targeting proliferating cells, preferably tumor cells, HSC, fibroblasts, endothelial cells and osteoblasts said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition according to the aspect of the invention just described to a subject or a tissue sample of a subject. In an alternative embodiment it also covers a method of targeting proliferating cells, preferably tumor cells, HSC, fibroblasts, endothelial cells and osteoblasts said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition according to the further aspect of the invention just described to a subject or a tissue sample of a subject. Alternatively it covers a method of therapy, diagnosis or prophylaxis of a disease related to proliferating cells, preferably tumor cells, HSC, fibroblasts, endothelial cells and osteoblasts, said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition according to the further aspect of the invention to a subject or a tissue sample of a subject. Specifically it

covers a method of therapy, diagnosis or prophylaxis of a disease related to HSC, said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition as described for the further aspect of the invention to a subject or a tissue sample of a subject. A method of therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis and sepsis, said method comprising administration in a pharmaceutically acceptable amount and form of a compound or a pharmaceutical composition as described for the further aspect of the invention to a subject or a tissue sample of a subject also falls within the scope of the invention.

This further aspect of the invention will be illustrated but not limited in the following examples.

EXAMPLE 5

Mannose 6-phosphate was covalently coupled to human serum albumin (HSA) in two steps. First, p-nitrophenyl-α-D-mannopyranoside (Sigma, St. Louis, USA) was phosphorylated according to standard procedures. The molecular weight (MW 381) and purity of the obtained crystalline product p-nitrophenyl-6-phospho-α-D-mannopyranoside was verified by mass spectrometry. Subsequently, the nitro-group was reduced with 10% palladium on active carbon (Aldrich Chemie GmbH, Steinheim, Germany) under hydrogen atmosphere of 1 atm. The obtained product p-aminophenyl-6-phospho-α-D-mannopyranoside was coupled to HSA by activation with thiophosgene. By variations in the molar ratio HSA: p-nitrophenyl-6-phospho-α-D-mannopyranoside, a series of neoglycoproteins ($M6P_x$-HSA) were obtained, x = 2, 4, 10, 21, or 28. The $M6P_x$-HSA preparations were further purified and characterized according to standard procedures.

A tracer dose of modified HSA (^{125}I labelled) was intravenously administered to normal and fibrotic rats (three weeks after bile duct ligation). Ten minutes after injection of these compounds, rats were sacrificed and all organs were removed. As can also be seen in figure 5, the degree of substitution of mannose 6-phosphate to HSA strongly influenced liver uptake. HSA with a low degree of sugar loading (x=2-10) accumulated for 2 ± 1% to 9 ± 0.5% in fibrotic rat livers, while the rest of the dose remained in the

circulation. An increase in the molar ratio of M6P:HSA up to 28 caused a gradual increase in liver accumulation (to 59 ± 9% of the dose).

In addition, the intrahepatic distribution of modified HSA was examined immunohistochemically. Modified HSA was administered to rats (10 mg/kg b.w.) and 10 minutes after the injection samples from the liver, spleen, kidney, and bone were histochemically examined. We observed that the more mannose 6-phosphate was linked to HSA, the higher the uptake was in HSC. Quantitative evaluation of liver sections ten minutes after administration of modified HSA revealed that M6P10-HSA accumulated for 19 ± 10% in HSC. In contrast, 69 ± 12% of the intrahepatic staining for M6P28-HSA was found in HSC, whereas 20 ± 6% was found in Kupffer cells and 17 ± 6% in endothelial cells. No uptake was detected in hepatocytes and bile duct epithelial cells. Also no staining for modified HSA was found in other organs.

EXAMPLE 6

$M6P_{21}$-bovine serum albumin (BSA) and $M6P_{28}$-HSA, synthesized and characterized according to standard procedures, were radiolabeled with ^{125}I. The intrahepatic uptake of these neo-glycoproteins was measured in human liver slices. These slices (± 10 mg liver tissue with a thickness of approximately 10 cells) were obtained from patients with normal liver function and from cirrhotic patients. Significant intrahepatic accumulation of radiolabeled BSA and HSA derivates was found within one hour after co-incubation with these slices, whereas unmodified BSA or HSA was not taken up by the human tissue samples (see figure 6).

EXAMPLE 7

Pyrrolidine-dithiocarbamate (PDTC, which is an inhibitor of the transcription factor NF-kappaB) was attached to $M6P_{28}$-HSA by coupling the carboxylic groups of PDTC to lysine groups of HSA according to standard procedures. This compound was administered to rats with liverfibrosis induced by bile duct ligation. Rats receiving this conjugate 1, 3 and 5 days after the bile duct ligation displayed less proliferation of HSC in the parenchymal area at day 7 as compared to rats receiving no treatment or PDTC alone after induction of fibrosis. HSC were demonstrated in cryostat sections with anti-desmine and anti-Glial Fibrillar Acidic Protein (GFAP) antibodies and standard indirect immunoperoxidase techniques.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 5. The organ distribution of radiolabeled $M6P^x$-HSA in fibrotic rats (three weeks after bile duct ligation), 10 minutes after intravenous administration of the modified HSA. x= 2, 4,10, 21, and 28. Note that proteins substituted with 2,4 or 10 M6P molecules per HSA remain in the blood, whereas proteins with high amounts of substitution accumulate in the liver.

Figure 6. Binding and uptake of radiolabeled $M6P_{28}$-HSA in human liver tissue at 4 degrees Celcius respectively 37 degrees Celsius. ^{125}I-labeled modified albumin was incubated with slices (10 mg) obtained from patients with a normal liver function. (TX = transplantation liver) or from patients with liver Cirrhosis (Cir).
Note the high accumulation of neo-glycoprotein in human liver slices as compared to native HSA.

CLAIMS

1. A compound comprising a carrier molecule, said carrier molecule being linked to a further molecule, said further molecule being at least one cyclic peptide, said cyclic peptide comprising in the cyclic peptide portion thereof at least one sequence encoding a cell receptor recognising peptide (RRP) and with the proviso the compound is not a naturally occurring receptor agonist or antagonist.

2. A compound according to claim 1, wherein the RRP is of a receptor specific for Hepatic Stellate Cells (HSC) or a receptor that is upregulated on HSC during disease.

3. A compound according to any of claims 1 or 2, wherein the RRP is of a receptor selected from the group of PDGF receptor, collagen type VI receptor, cytokine receptor(s) such as TGFß, TNFα and interleukin 1ß.

4. A compound according to any of claims 1-3, wherein the RRP is of a collagen type VI receptor, cytokine receptor(s) such as TGFß, TNFα and interleukin 1ß.

5. A compound according to claim 4, wherein the cyclic portion of the cyclic peptide comprises at least the amino acid sequence RGD or KPT in the cyclic portion thereof.

6. A compound according to any of claims 4 or 5, wherein the cyclic portion of the cyclic peptide comprises at least an amino acid sequence selected from X*YRGDYX* and X*YKPTYX*, wherein X* represents the location of cyclisation and Y represents at least one amino acid or a sequence of amino acids up to a length such that the receptor binding capacity of the cyclic peptide is retained.

7. A compound according to any of claims 4-6, wherein the cyclic portion of the cyclic peptide comprises at least an amino acid sequence selected from X*YRGDYX* and X*YKPTYX*, wherein X* represents the location of cyclisation and Y represents at least one amino acid or a sequence of amino acids up to a length such

that the receptor binding capacity of the cyclic peptide is retained and wherein X* represents the location of attachment to the carrier molecule.

8. A compound according to any of claims 1-7, wherein the RRP is of a collagen type VI receptor and the cyclic portion of the cyclic peptide comprises the amino acid sequence X*GRGDSPX*.

9. A compound according to any of claims 1-7, wherein the RRP is of a interleukin 1 beta receptor and the cyclic portion of the cyclic peptide comprises the amino acid sequence X*DKPTLX*.

10. A compound according to any of claims 1-9, wherein X* is a cysteine residue.

11. A compound according to any of claims 1-3, wherein the RRP is of a PDGF receptor and the cyclic portion of the cyclic peptide comprises an amino acid sequence sekected from X*SRNLIDCX* and X*RKKPX*, wherein X* represents the location of cyclisation.

12. A compound according to claim 11, wherein the RRP is of a PDGF receptor and the cyclic portion of the cyclic peptide comprises an amino acid sequence selected from X*SRNLIDCX* and X*RKKPX*, wherein X* represents the location of cyclisation and attachment to the carrier molecule.

13. A compound according to claim 11 or 12, wherein the RRP is of a PDGF receptor and the cyclic portion of the cyclic peptide comprises an amino acid sequence selected from X*SRNLIDCX*, and X*RKKPX*, wherein X is a cysteine residue.

14. A compound according to any of the preceeding claims wherein the cyclic portion of the cyclic peptide comprises multiple receptor binding sequences.

15. A compound according to any of the preceeding claims wherein the cyclic portion of the cyclic peptide comprises multiple receptor binding sequences directed at at

least two different types of receptors.

16. A compound according to any of the preceeding claims, comprising multiple cyclic peptides directed at the same or different types of receptors.

17. A compound according to any of the preceeding claims, wherein the carrier molecule is selected from the group of carrier molecules consisting of proteins, oligo or polypeptides, immunoglobulins or parts thereof, oligonucleotides, disaccharides, polysaccharides, biodegradable synthetic polymers, liposomes, lipid particles, biocompatible polymers in the form of microspheres or nanoparticles.

18. A compound according to any of the preceeding claims, wherein the carrier molecule is linked to the cyclic peptide via a biodegradable spacer.

19. A compound according to any of the preceeding claims, wherein the carrier molecule is linked to more than one cyclic peptide, suitably 5-15 cyclic peptides as defined in any of the preceding claims.

20. A compound according to any of the preceeding claims, wherein the carrier molecule comprises free reactive groups such as hydroxyl, amine or sulphate.

21. A compound according to any of the preceeding claims, wherein the carrier molecule comprises additional drugs or chemicals linked thereto.

22. A pharmaceutical composition comprising a compound according to any of the preceeding claims as targeting ingredient and any pharmaceutically acceptable carrier.

23. A pharmaceutical composition comprising a compound according to any of the claims 1-21 as pharmaceutically active ingredient and any pharmaceutically acceptable additional carrier.

24. A pharmaceutical composition comprising a compound according to any of the claims 1-21 as pharmaceutically active ingredient and any pharmaceutically

acceptable carrier, wherein the compound further comprises a drug biodegradably attached thereto.

25. A pharmaceutical composition comprising a compound according to any of the claims 1-21 as pharmaceutically active ingredient and any pharmaceutically acceptable carrier, wherein the compound further comprises a diagnostic marker attached thereto.

26. A pharmaceutical composition according to any of claims 22-25 in a medicinal dosage form.

27. A pharmaceutical composition according to any of claims 22-26 in a systemically acceptable form.

28. Use of a compound according to any of claims 1-21 as active targeting ingredient for manufacturing a pharmaceutical composition according to any of claims 22-27 for therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis and sepsis.

30. Use of a compound according to any of claims 1-21 as active targeting ingredient for manufacturing a pharmaceutical composition according to any of claims 22-27 for therapy, prophylaxis or diagnosis of a disease related to proliferation of HSC.

30. A method of targeting HSC, said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 1-21 or a pharmaceutical composition according to any of claims 22-27 to a subject or a tissue sample of a subject.

31. A method of therapy, diagnosis or prophylaxis of a disease related to HSC, said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 1-21 or a pharmaceutical composition

according to any of claims 22-27 to a subject or a tissue sample of a subject.

32. A method of therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis and sepsis, said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 1-21 or a pharmaceutical composition according to any of claims 22-27 to a subject or a tissue sample of a subject.

33. A compound capable of recognising and binding a mannose 6 phosphate receptor said compound comprising a carrier molecule linked to a molecule capable of recognising and capable of binding mannose-6-phosphate receptor, said molecules recognising and capable of binding mannose-6-phosphate receptor being present on the carrier molecule in at least an amount sufficient to occupy at least 20% of the carrier molecule linking sites for said molecules recognising and capable of binding mannose-6-phosphate receptor, with the proviso the compound is not latent tumor growth factor beta, thyroglobulin or a lysosomal protein.

34. A compound capable of recognising and binding a mannose 6 phosphate receptor said compound comprising a carrier molecule linked to a molecule capable of recognising and capable of binding mannose-6-phosphate receptor, said molecules recognising and capable of binding mannose-6-phosphate receptor being present on the carrier molecule in at least an amount sufficient to occupy at least 20% of the carrier molecule linking sites for said molecules recognising and capable of binding mannose-6-phosphate receptor, with the proviso the compound is not a naturally occurring protein with terminal mannose 6 phosphate residues.

35. A compound according to claim 33 or 34 wherein the carrier molecule is selected from the group consisting of proteins, oligo or polypeptides, immunoglobulins or parts thereof, oligonucleotides, disaccharides, polysaccharides, biodegradable synthetic polymers, liposomes, lipid particles, biocompatible polymers in the form of microspheres or nanoparticles.

36. A compound according to any of the preceeding claims, wherein the molecule capable of recognising and capable of binding mannose-6-phosphate receptor is mannose 6 phosphate.

37. A compound according to any of the preceeding claims, wherein said compound comprises a carrier molecule linked to a molecule capable of recognising and capable of binding mannose-6-phosphate receptor, said molecule recognising and capable of binding mannose-6-phosphate receptor being present on the carrier molecule in at least an amount sufficient to occupy at least 20% of the carrier molecule linking sites for said molecules recognising and capable of binding mannose-6-phosphate receptor, with the proviso the compound is not a naturally occurring protein with terminal mannose 6 phosphate residues.

38. A compound according to any of the preceeding claims wherein the carrier molecule is selected from endogenous plasma proteins e.g. albumin, lactoferrin, alkaline phosphatase, superoxide dismutase, alpha2 macroglobulin and fibronectin.

39. A compound according to any of the preceeding claims wherein at least 10 molecules capable of recognising and capable of binding mannose-6-phosphate receptor are present linked to the carrier molecule.

40. A pharmaceutical composition comprising a compound according to any of the claims 33-39 as targeting ingredient and any pharmaceutically acceptable carrier.

41. A pharmaceutical composition comprising a compound according to any of the claims 33-39 as pharmaceutically active ingredient and any pharmaceutically acceptable additional carrier.

42. A pharmaceutical composition comprising a compound according to any of the claims 33-39 as pharmaceutically active ingredient and any pharmaceutically acceptable carrier, wherein the compound further comprises a drug biodegradably attached thereto.

43. A pharmaceutical composition comprising a compound according to any of the claims 33-39 as pharmaceutically active ingredient and any pharmaceutically acceptable carrier, wherein the compound further comprises a diagnostic marker attached thereto.

44. A pharmaceutical composition according to any of claims 40-43 in a pharmaceutical dosage form.

45. A pharmaceutical composition according to any of claims 40-44 in a systemically acceptable form.

46. Use of a compound according to any of claims 33-39 as active targeting ingredient for manufacturing a pharmaceutical composition according to any of claims 40-45 for therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis, sepsis.

47. Use of a compound according to any of claims 33-39 as active targeting ingredient for manufacturing a pharmaceutical composition according to any of claims 40-45 for therapy, prophylaxis or diagnosis of any of the following pathological conditions cell proliferation associated pathology e.g. tumors, a disease related to proliferation of HSC, fibroblast proliferation associated pathology, endothelial cell proliferation associated pathology and osteoblast proliferation associated pathology.

48. A method of targeting proliferating cells, preferably tumor cells, HSC, fibroblasts, endothelial cells and osteoblasts said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 34-39 or a pharmaceutical composition according to any of claims 40-45 to a subject or a tissue sample of a subject.

49. A method of targeting proliferating cells, preferably tumor cells, HSC, fibroblasts, endothelial cells and osteoblasts said method comprising administration in a

pharmaceutically acceptable amount and form of a compound according to any of claims 33-39 or a pharmaceutical composition according to any of claims 40-45 to a subject or a tissue sample of a subject.

50. A method of therapy, diagnosis or prophylaxis of a disease related to proliferating cells, preferably tumor cells, HSC, fibroblasts, endothelial cells and osteoblasts, said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 33-40 or a pharmaceutical composition according to any of claims 41-46 to a subject or a tissue sample of a subject.

51. A method of therapy, diagnosis or prophylaxis of a disease related to HSC, said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 33-39 or a pharmaceutical composition according to any of claims 40-45 to a subject or a tissue sample of a subject.

52. A method of therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, atherosclerosis, rheumatoid arthritis, Crohns disease, colitis ulcerosa, glomerulonephritis, lung fibrosis and sepsis, said method comprising administration in a pharmaceutically acceptable amount and form of a compound according to any of claims 33-39 or a pharmaceutical composition according to any of claims 40-45 to a subject or a tissue sample of a subject.

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Fig-1a

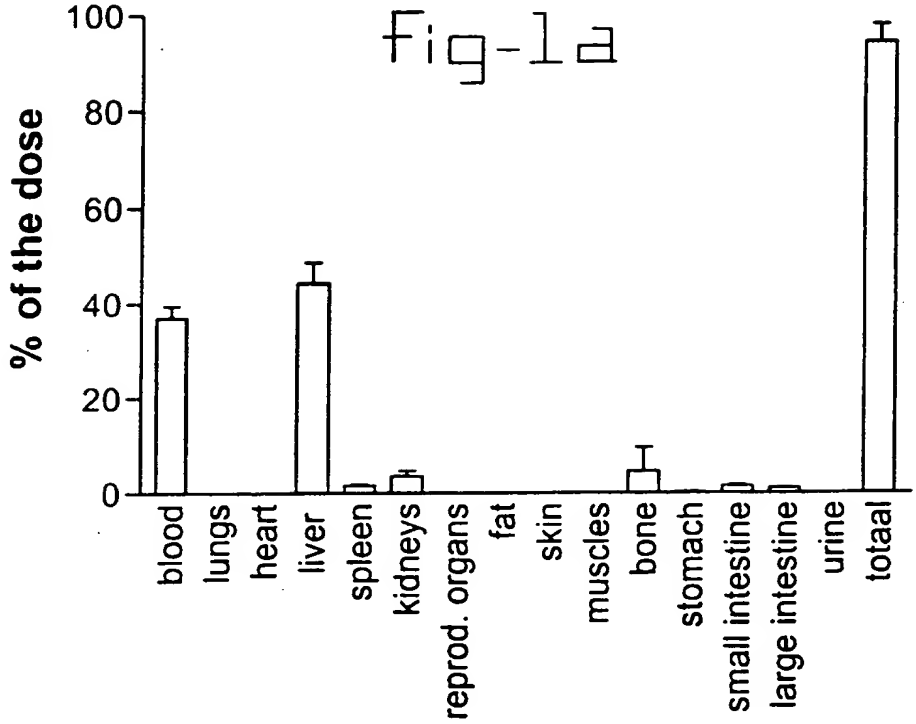

% of the dose
100
80
60
40
20
0
blood
lungs
heart
liver
spleen
kidneys
reprod. organs
fat
skin
muscles
bone
stomach
small intestine
large intestine
urine
totaal

Fig-1b

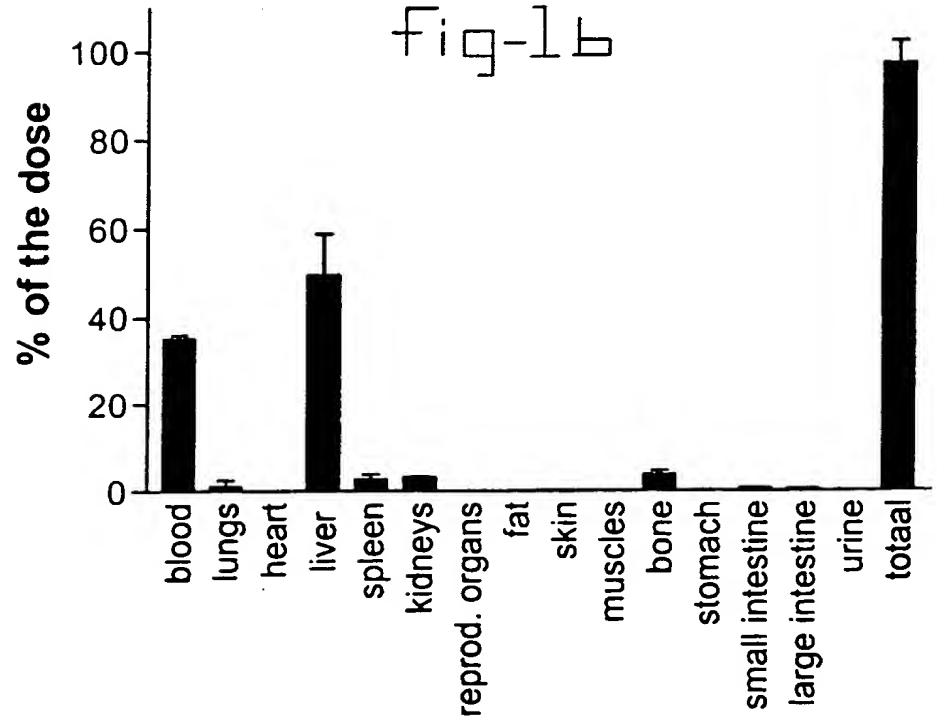
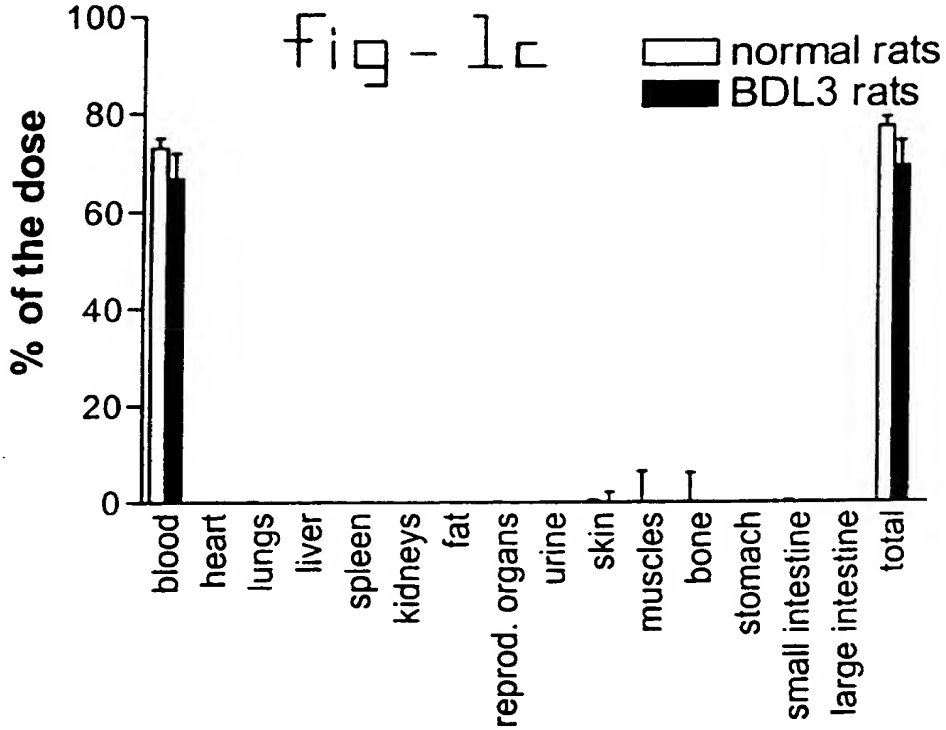

% of the dose
100
80
60
40
20
0
blood
lungs
heart
liver
spleen
kidneys
reprod. organs
fat
skin
muscles
bone
stomach
small intestine
large intestine
urine
totaal

fig - 1c


normal rats
BDL3 rats
% of the dose
100
80
60
40
20
0
blood
heart
lungs
liver
spleen
kidneys
fat
reprod. organs
urine
skin
muscles
bone
stomach
small intestine
large intestine
total

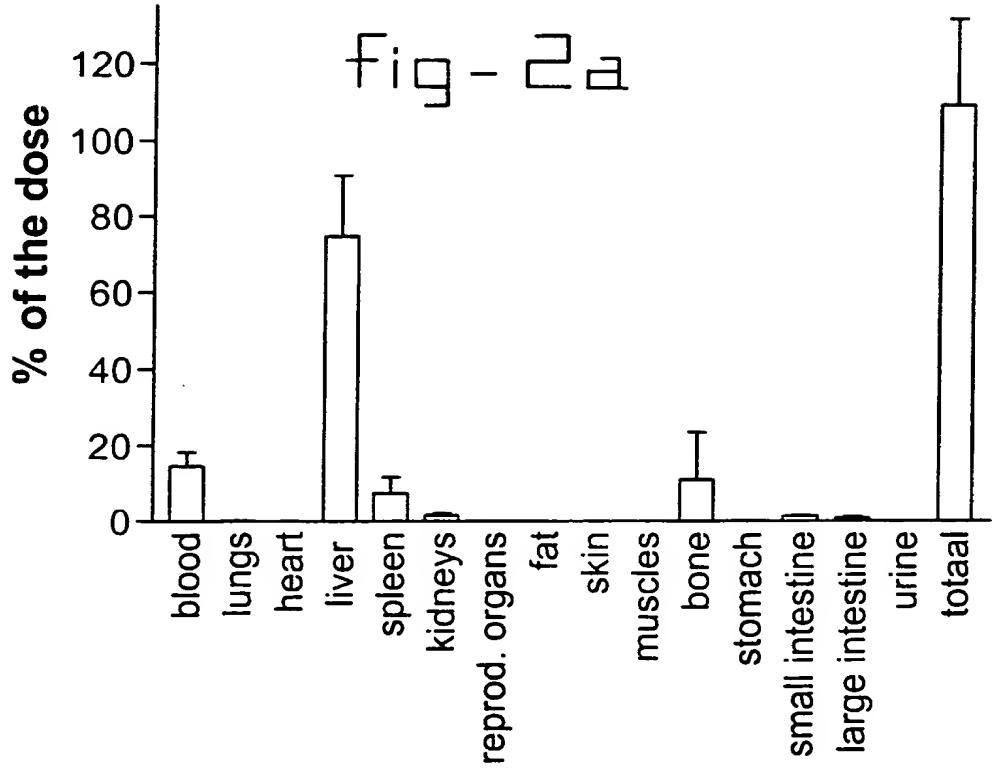

% of the dose
120
100
80
60
40
20
0
blood
lungs
heart
liver
spleen
kidneys
reprod. organs
fat
skin
muscles
bone
stomach
small intestine
large intestine
urine
totaal

Fig - 2a

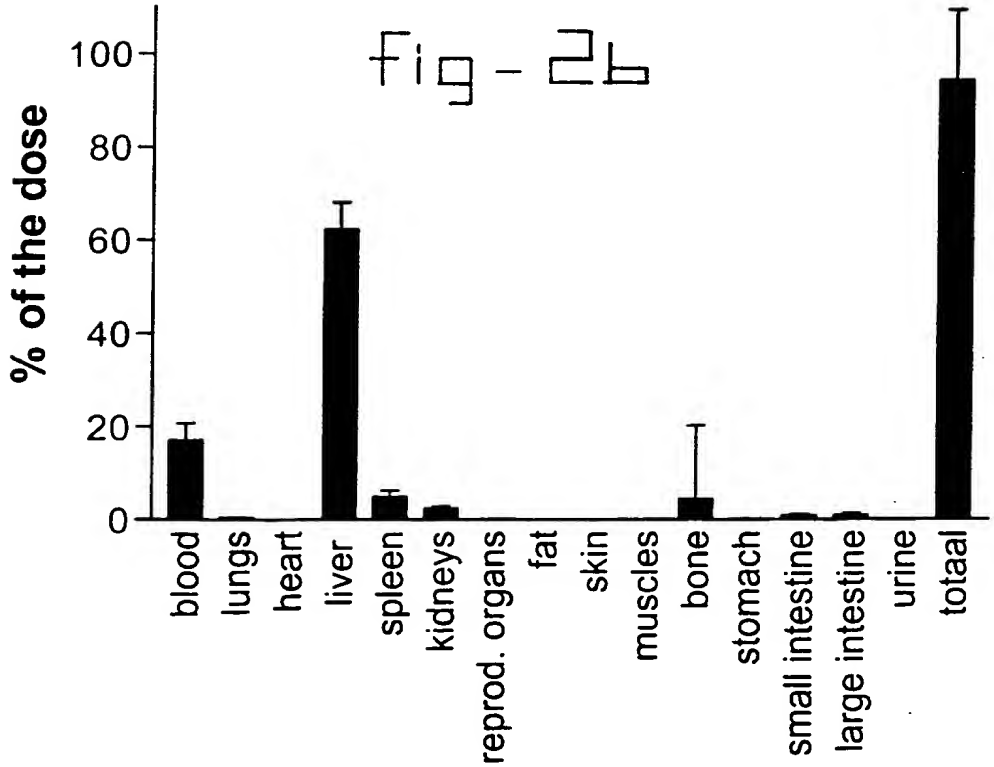

% of the dose
100
80
60
40
20
0
blood
lungs
heart
liver
spleen
kidneys
reprod. organs
fat
skin
muscles
bone
stomach
small intestine
large intestine
urine
totaal

Fig - 2b

fig - 3a

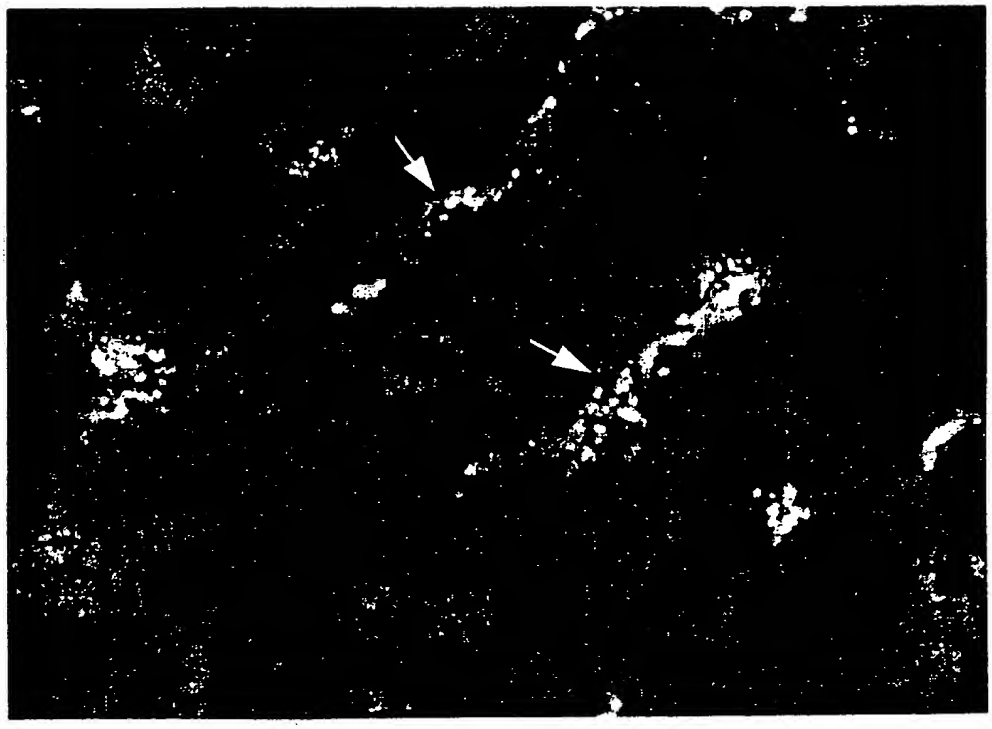


fig - 3b

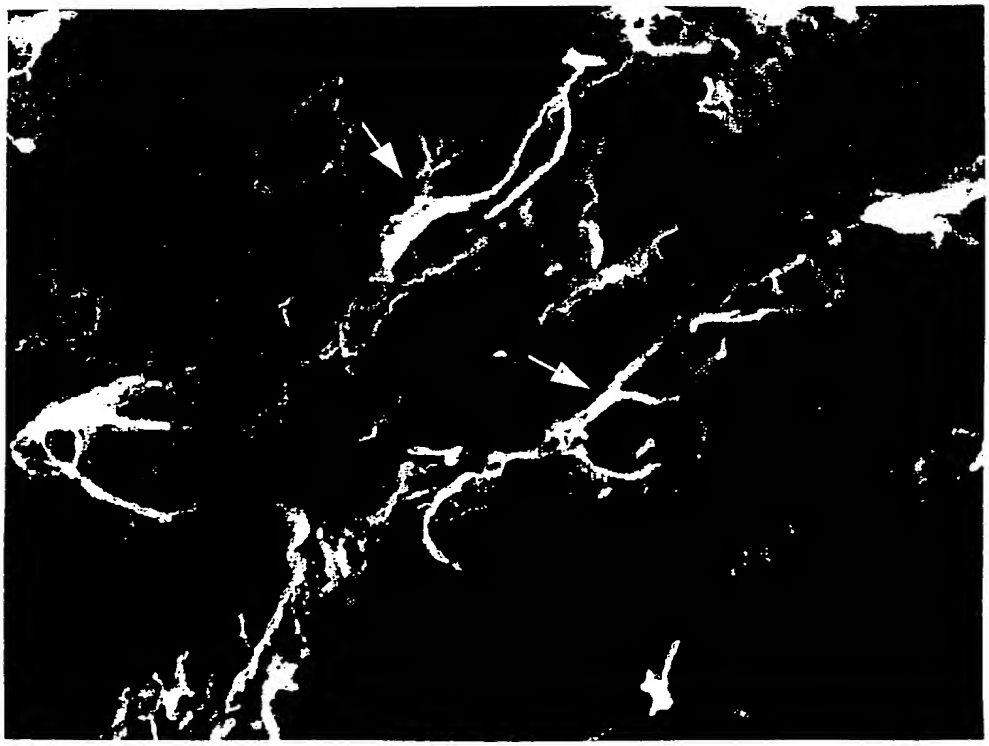


Fig - 4

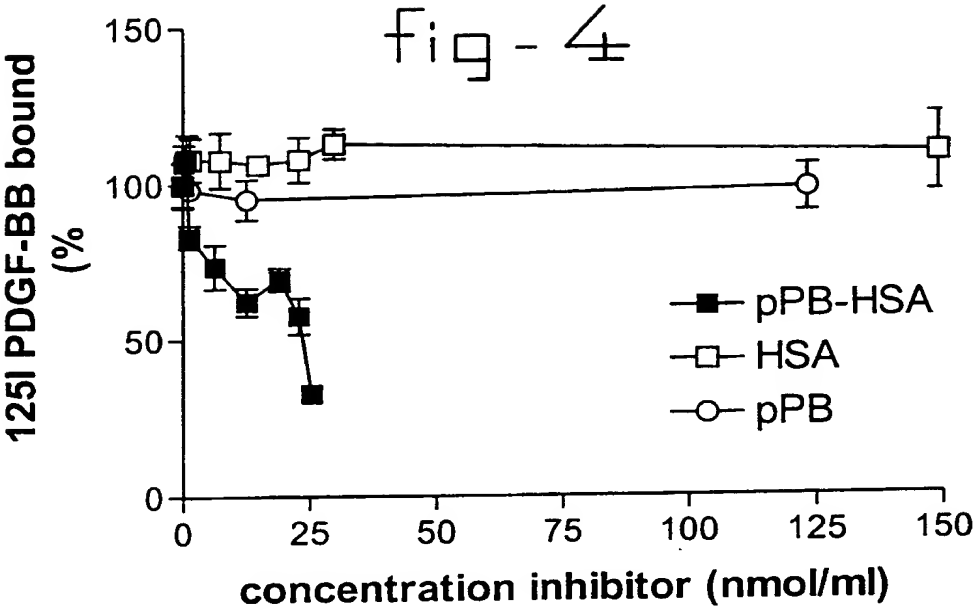

125I PDGF-BB bound (%
150
100
50
0
0
25
50
75
100
125
150
concentration inhibitor (nmol/ml)
pPB-HSA
HSA
pPB

Fig - 5

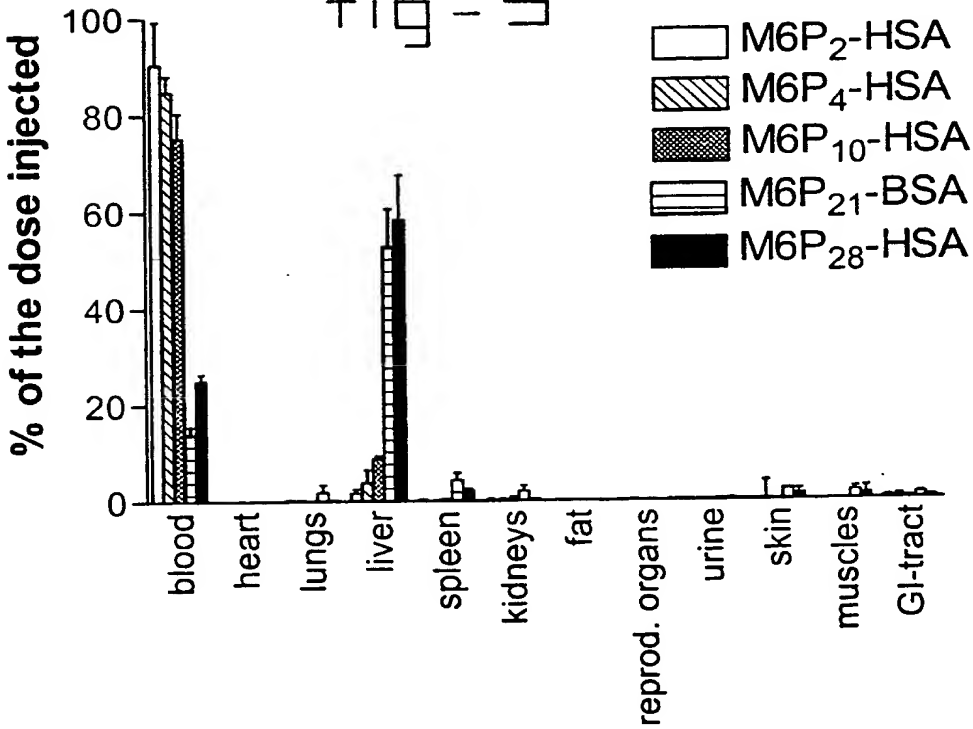
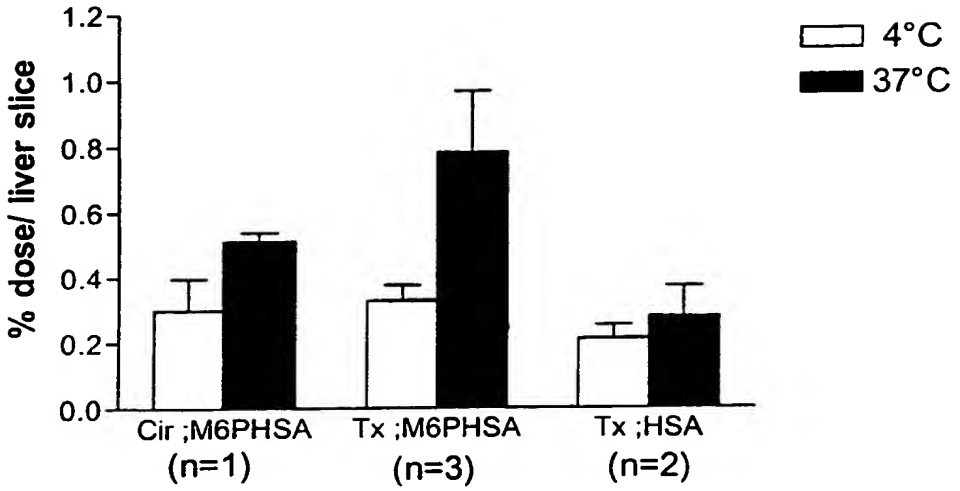

% of the dose injected
100
80
60
40
20
0
blood
heart
lungs
liver
spleen
kidneys
fat
reprod. organs
urine
skin
muscles
GI-tract
M6P2-HSA
M6P4-HSA
M6P10-HSA
M6P21-BSA
M6P28-HSA

Fig - 6


% dose/ liver slice
1.2
1.0
0.8
0.6
0.4
0.2
0.0
4°C
37°C
Cir ;M6PHSA
(n=1)
Tx ;M6PHSA
(n=3)
Tx ;HSA
(n=2)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
BO 42135		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 98/ 00579	08/10/1998	
Applicant		
STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PEPTIDE-BASED CARRIER DEVICES FOR STELLATE CELLS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATION. EARCH REPORT

International application No.
[redacted]/NL 98/00579

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 30-32, 48-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claim(s) 31-32, 50-52 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 98/00579

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BELJAARS, LEONIE (1) ET AL: "The development of novel albumin carriers to hepatic stellate cells by application of cyclopeptide moieties recognizing collage type VI and platelet derived growth factor receptors." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 313A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE , XP002108150 See page 313A, abstract 602 --- -/--	1-52

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 1999	02/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 98/00579

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BELJAARS, LEONIE ET AL: "Mannose 6-phosphate modified albumin accumulates in hepatic stellate cells: Potential application as an antifibroti drug carrier." HEPATOLOGY, (OCT., 1998) VOL. 28, NO. 4 PART 2, PP. 233A. MEETING INFO.: BIENNIAL SCIENTIFIC MEETING OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER AND THE 49TH ANNUAL MEETING AND POSTGRADUATE COURSES OF THE AMERICAN ASSOCIATION FOR THE , XP002108151 See page 233A, abstract 282 ---	1-52
Y	DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AN=129:260816, DELFORGE, DOMINIQUE ET AL: "Design of a synthetic adhesion protein by grafting RGD tailed cyclic peptides on bovine serum albumin" XP002108152 see abstract & LETT. PEPT. SCI. (1998), 5(2-3), 87-91 CODEN: LPSCEM;ISSN: 0929-5666,1998, ---	1-52
Y	EP 0 844 252 A (REMACLE JOSE) 27 May 1998 see column 2, line 45 - line 58; claims 1,11	1-52
X	see page 15, line 16 - line 39 see column 4, line 33 - line 53 ---	1
A	WO 97 46099 A (NEORX CORP) 11 December 1997 see page 27, line 25 - page 28, line 10 -----	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC[redacted] 98/00579

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0844252 A	27-05-1998	NONE	
WO 9746099 A	11-12-1997	EP 0906015 A	07-04-1999